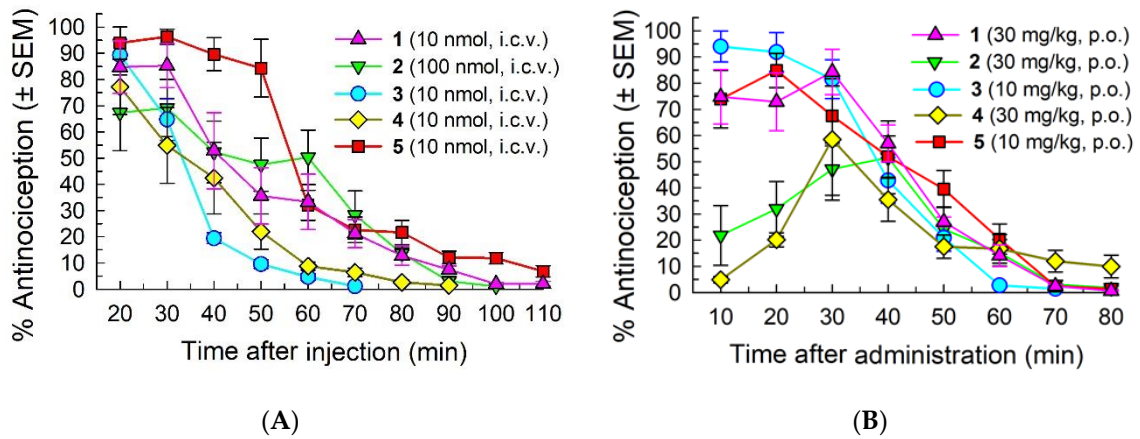
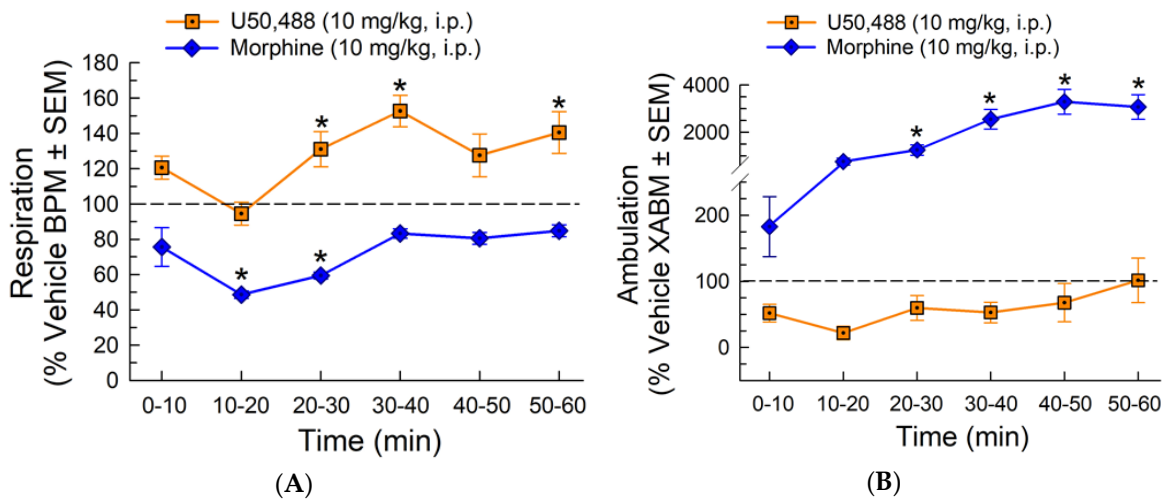


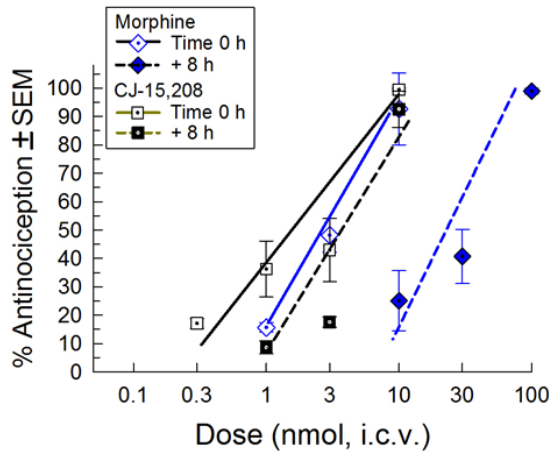
## Supplementary Material



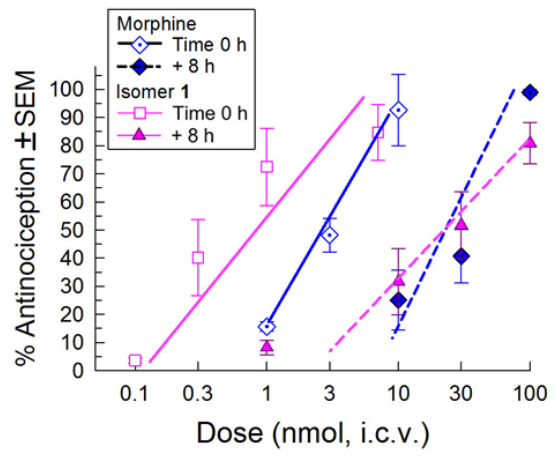
**Figure S1.** Time-course of antinociceptive activity in the 55 °C warm-water tail-withdrawal assay following (A) i.c.v. administration and (B) oral administration in C57Bl/6J mice of a maximally efficacious dose. Points represent average % antinociception ± SEM from 4-16 mice for each set presented.



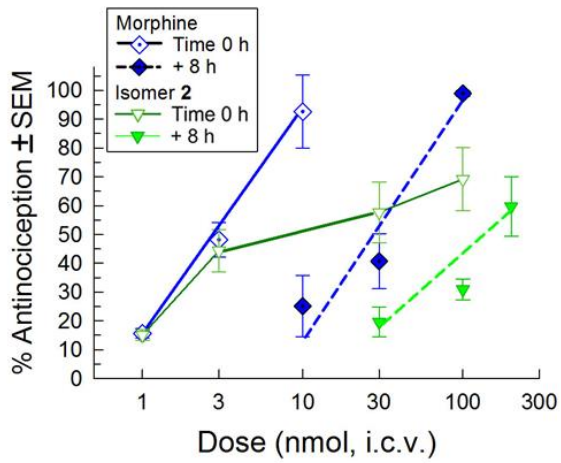
**Figure S2.** Effects of the U50,488 or morphine on (A) respiration and (B) ambulation in C57BL76J mice. Respiration and ambulation were monitored after administration of U50,488 or morphine (10 mg/kg, i.p.) using the CLAMS/Oxymax system. Data from 9-18 mice presented as % vehicle response ± SEM; breaths per minute, BPM (A) or ambulation, XAMB (B). \*significantly different from response of saline alone ( $p < 0.05$ ); two-way RM ANOVA with Dunnett's multiple comparison *post hoc* test.



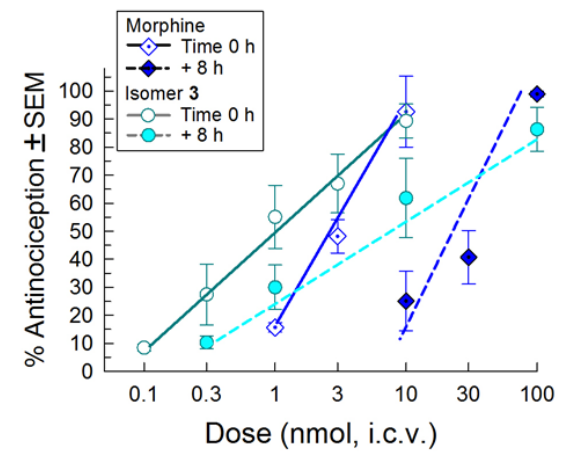
(A)



(B)

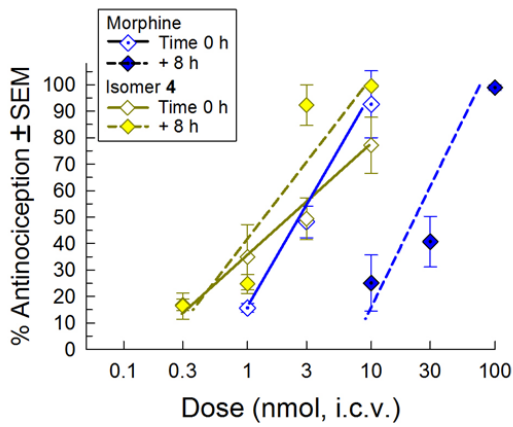


(C)

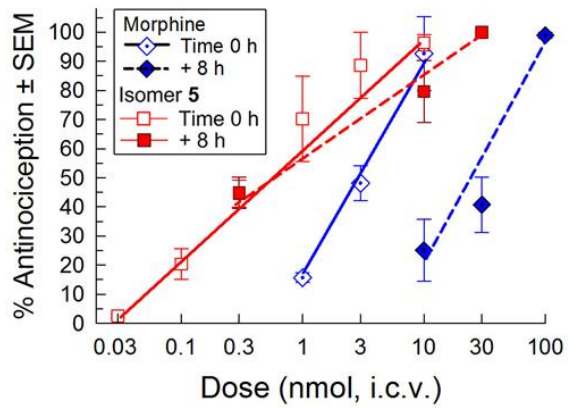


(D)

Figure S3. Cont.

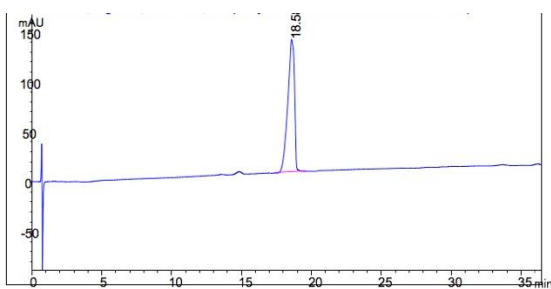


(E)

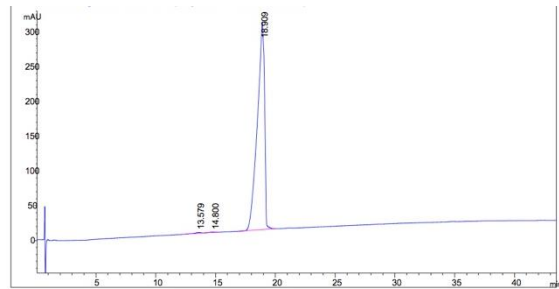


(F)

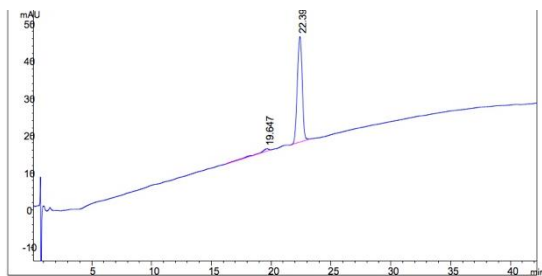
**Figure S3.** Evaluation of acute antinociceptive tolerance in the 55 °C warm-water tail-withdrawal assay following i.c.v. administration of morphine, (A) CJ-15,208, (B) 1, (C) 2, (D) 3, (E) 4 or (F) 5. All points represent antinociception at peak response in naïve mice (Time 0 h) and mice that were previously administered an ED<sub>50</sub> dose of test compound (as listed) prior to additional administration of a graded dose of test compound eight hours later (Time 8 h). Points represent average % antinociception ± SEM from 8-16 mice for each set presented.



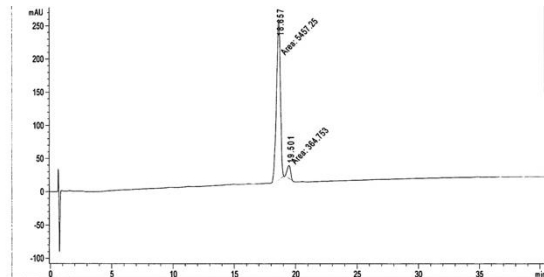
(A)



(B)

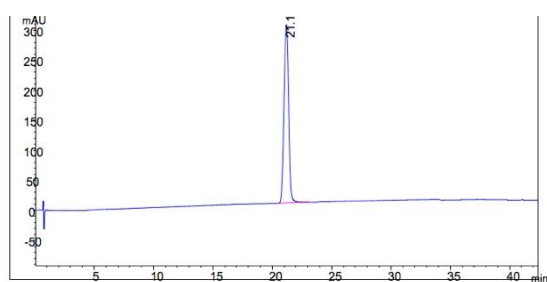


(C)



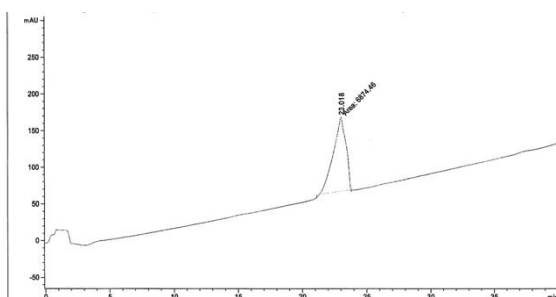
(D)

**Figure S4. Cont.**

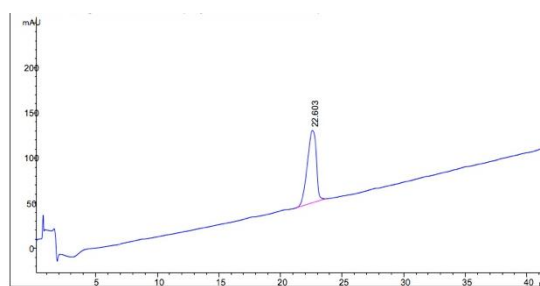


**(E)**

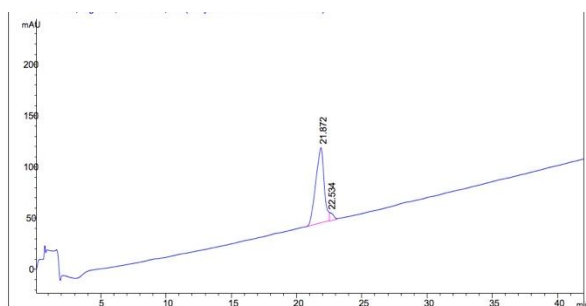
**Figure S4.** HPLC chromatograms of the peptides in 15–55% MeCN over 40 min with 0.1% TFA, detection at 214 nm, (A) 1, (B) 2, (C) 3, (D) 4 and (E) 5



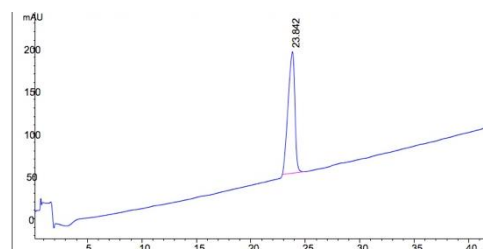
**(A)**



**(B)**



**(C)**



**(D)**

**Figure S5.** HPLC chromatograms of the peptides in 30–70% MeOH over 40 min with 0.1% TFA, detection at 230 nm, (A) 1, (B) 3, (C) 4 and (D) 5